Quantum similarity of isosteres: coordinate versus momentum space and influence of alignment

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QUANTUM SIMILARITY OF ISOSTERES

COORDINATE VERSUS MOMENTUM SPACE AND INFLUENCE OF ALIGNMENT

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ABSTRACT

Molecular quantum similarity was studied for a set of peptide isosteres analyzed before by Boon et al. (*Chemical Physics Letters*, 1998, 295 122). Overlap and Coulomb similarity measures in coordinate space were calculated using the TGSA (Topo-Geometrical Superposition Algorithm) algorithm for the alignment of molecules instead of the one used in the previous work, and a comparison between the superposition methods was made. Overlap and first order moment similarity indices in momentum space are computed for the same alignment. The results illustrate the importance of the alignment algorithm for the evaluation of molecular similarity in a given set of molecules and show that the degree of similarity depends dramatically on the similarity measure used and the space in which the similarity is computed. For a small set of propane derivatives where the similarity ranking is known from drug design, only momentum space similarity integrals give the expected similarity ordering.

Key words: Molecular similarities, TGSA algorithm, peptide isosteres, ASA approach, quantum similarity, momentum space.

INTRODUCTION

Similarity is a cornerstone in human observation and the subsequent interpretation of the observed. It is a ubiquitously used concept, especially in chemistry, where it forms the basis of e.g., the different classifications of substances in acids or bases and the periodic system of elements [1-2]. In this way, in the past decades there have been many efforts to calculate in a quantitative manner the resemblance between molecules. Method to express similarity between molecules use so-called molecular descriptors whose complexity ranges from global molecular properties like molecular mass to presence/absence data or feature counts up to methods that rely on 3D molecular field comparison [3].

In 1980, Carbó and coworkers proposed a new method for the evaluation of the resemblance between molecules, using only the electron densities of molecules as comparative tool [4]. In DFT theory, the electron density contains all information that can be extracted from a system, and in this sense, the use of this property is the most conclusive method for calculating similarity. Alternatively, quantum similarity can be extended to the use of the shape function or so-called conceptual DFT quantities [5]. Quantum similarity measures in coordinate space depend, for every property chosen as comparative tool, on the relative position in three dimensional space of the molecules being compared [6,7]. In this sense, different conclusions on the degree of similarity can be reached depending on the alignment scheme; it is therefore important to carefully choose an alignment method based on the goal of the study. For example, one could align molecules based on a structural motif such as a pharmacophore. In the present study, the Topo-Geometrical Superposition Algorithm (TGSA), introduced by Gironés et al. [6,8] was used. TGSA can be used for systems with some common (sub)structure and can align similar functional groups between molecules under comparison in a way consistent with biochemical reality as

similar functional groups tend to react with the same part of a given receptor.

In this paper we make a comparison of two alignment methods over the same set of molecules, a group of peptide isosteres, molecules that can mimic certain properties of peptides because of the resemblance of a bond to the amide bond in the parent peptide. To avoid the specific nucleophilic attack of enzymes toward the amide bond, Tourwé et al. replaced the R–CO–NH–R´ motif by different isosteres consisting of a set of atoms that can mimic the sterical and/or electronical properties of the peptide [9-11]. All these features are desirable in peptide alike drugs such that they can remain stable longer in the human body [12,13]. The isosteres synthesized by Tourwé et al. were theoretically studied before by Boon et al. using a user determined molecular alignment [14]. Given the dependence of degrees of molecular similarity on the molecular alignment, the first aim of the present paper is to examine the effect of the alignment method on the similarity measures in these molecules.

Most of the work done up to now in quantum similarity focused on coordinate space although an interesting line of work originating mainly from Allan and Cooper and co-workers [15-17] proposed to examine molecular quantum similarity in momentum space. This has the advantage that the impact of the alignment issue can be reduced substantially as the translation of the molecules as in coordinate space alignment can be removed. Another significant advantage is that the momentum space density is dominated by the valence electrons whereas in the case of coordinate space quantum similarity the alignment and similarity measures are dominated by the core electrons. The second aim of the paper is therefore to examine what the differences are in the similarity indices obtained in coordinate and momentum space. The case of the propane derivatives studied previously by Allan and Cooper [15] is used to compare similarity indices arising from similarities computed in both spaces. For this case, the correct similarity ordering is known from biological activity data so the third aim of the paper is to examine whether all similarity approaches do lead to the expected ranking.

MOLECULAR QUANTUM SIMILARITY

As reviews on quantum similarity can be found elsewhere (see, for example, references [1-2,18-22]), only general definitions will be given at this point. Quantum similarity provides a quantitative measure of the resemblance between two quantum objects, A and B [4]. A quantum similarity measure in coordinate space (rQSM) involving these two objects, z_{AB} can be constructed using their corresponding density functions. Both density functions can be multiplied and integrated over the respective electronic coordinates in a convenient domain, weighted by a positive definite operator [2,18]. That is,

$$z_{AB} = \int \rho_A(\mathbf{r}_1)\Omega(\mathbf{r}_1,\mathbf{r}_2)\rho_B(\mathbf{r}_2)d\mathbf{r}_1 d\mathbf{r}_2 \qquad (1)$$

Where $\rho_A(\mathbf{r}_1)$ and $\rho_B(\mathbf{r}_1)$ are the first-order molecular electron density functions of the two molecular structures being compared and $\Omega(\mathbf{r}_1,\mathbf{r}_2)$ is a positive definite operator. The integrations are carried out over a proper domain or, as usual, over the entire space where molecular structures are supposed to be embedded [4]. Since electron densities and the chosen operator $\Omega(\mathbf{r}_1,\mathbf{r}_2)$ are positive definite, rQSMs are always positive real numbers. Depending on the form of the operator, different types of molecular quantum similarity measures can be defined [2,18]. The most used rQSM is the so-called overlap rQSM, in which the operator is Dirac's delta function:

$$z_{AB} = \int\int \rho_A(\mathbf{r}_1)\delta(\mathbf{r}_1-\mathbf{r}_2)\rho_B(\mathbf{r}_2)d\mathbf{r}_1 d\mathbf{r}_2 = \int \rho_A(\mathbf{r})\rho_B(\mathbf{r})d\mathbf{r} \qquad (2)$$

This kind of QSM is simply the quantitative measure of the superposition of two molecular density functions and obviously depends on the alignment of the two molecules under comparison [6,7]. The second most known similarity measure is the Coulomb QSM, where the Coulomb operator $|\mathbf{r}_1-\mathbf{r}_2|^{-1}$ is employed.

Once the molecular quantum similarity matrix (MQSM) for a given set of molecules has been computed, a normalization of the MQSM elements can be done by transforming them into so-called quantum similarity indices, among which the best known is the Carbó similarity index [2,4], obtained as:

$$R_{AB} = \frac{z_{AB}}{\sqrt{z_{AA} z_{BB}}} \tag{3}$$

providing a weighted similarity measure between 0 and 1. The closer the value to one, the higher the degree of similarity. Alternatively, one can also use a distance related measure which often gives somewhat more detailed information. In general we introduce these distance measures via their square as [2]:

$$\begin{aligned} D^{r}_{AB}(\Omega) &= \int d\mathbf{r}_1\, d\mathbf{r}_2 \left[\rho_A(\mathbf{r}_1) - \rho_B(\mathbf{r}_1)\right] \Omega(\mathbf{r}_1, \mathbf{r}_2) \left[\rho_A(\mathbf{r}_2) - \rho_B(\mathbf{r}_2)\right] \\ &= z_{AA}(\Omega) + z_{BB}(\Omega) - 2 z_{AB}(\Omega) \end{aligned} \tag{4}$$

Note that only in case of Dirac's delta function, a true squared Euclidean distance is obtained. As stated above, similarity measures depend on the relative position of the molecules under comparison. Here, the Topo-Geometrical Superposition Approach (TGSA) [6,8] has been used to perform the needed pairwise molecular alignments. This molecular superposition method overlays the involved molecules according to the maximal common substructure shared by them.

As mentioned above, Allan and Cooper, in an attempt to reduce the impact of core electron densities and alignment, pursued quantum similarity in momentum space rather than coordinate space [15-17]. Several interesting applications appeared, including a case of isosteres of propane. The above QSM can be defined in a very similar way in momentum space to produce mQSM, although the most often used ones are either overlap mQSM and mQSM where the operator is the moment to some power k. Both QSM can be written as special cases of:

$$\begin{aligned} D^{m}_{AB}(k) &= \int d\mathbf{p} \left[\pi_A(\mathbf{p}) - \pi_B(\mathbf{p})\right] p^k \left[\pi_A(\mathbf{p}) - \pi_B(\mathbf{p})\right] \\ &= z^{m}_{AA}(k) + z^{m}_{BB}(k) - 2 z^{m}_{AB}(k) \end{aligned} \tag{5}$$

Note that here $\pi_A(\mathbf{p})$ is the momentum space one electron density for molecule A. In the present work we make use of indices with k=0 (overlap mQSM) and k=1.

COMPUTATIONAL DETAILS

In this study we considered first the same series of peptide isosteres used by Boon et al. in [14]: R–CH=CH–R´, R–CF=CH–R´, R–CH_2–CH_2–R´, R–CH_2–S–R´, R–CO–CH_2–R´ and R–CH_2–NH–R´, by incorporating the peptide bond in a model system R–CO–NH–R, where R=CH_3 (Figure 1).

Boon et al. performed only overlap QSM calculations in coordinate space and so their results can depend to large extent on the alignment scheme. In their study alignment was performed in three different ways in order to establish the relative position of the molecules. In all three cases, first the center of the reference peptide bond taken as half of the bond length was put at the origin of a Cartesian coordinate system. The first method consists of putting the first atom of the central bond of both molecules together, whereas in the second method the second atom of the central bond of both molecules is forced to coincide. In the third method, the centre of both central bonds is put at the origin

In the present work, due to the great resemblance in the molecular set, we opted to superpose the molecules according to the common substructures in the molecules (Figure 2); we chose this method to account for the nature of the central bond of the molecule (the amide bond in the case of a peptide), including the side chain and vice versa. Molecular alignment is done using the TGSA algorithm, used ubiquitously in molecular quantum similarity work. In the TGSA algorithm molecules are aligned on the common atomic dyads and triads and the best alignment is chosen based on the best fit. At the end of the algorithm the overlap and Coulomb rQSM are computed using the atomic shell approximation (ASA) [23-25] to build approximate electron densities. In this approximation, the molecular density is expressed as a sum of atomic densities located in the same locations in space as the molecule. The spherically symmetric ASA densities are expressed in terms of a linear combination of 1S gaussian type functions fitted to ab initio atomic densities, thereby giving rise to quite simple integrals. QSM from ASA densities have been shown to be virtually indistinguishable from those computed with the electron density as obtained from an ab initio calculation [26]. Nevertheless ab initio rQSM have been

computed as well from B3LYP/6-31G* calculations. From these ab initio rQSM, Carbó similarity indices were obtained as well as $D_{AB}^{r}(\Omega)$ measures. This procedure allows a direct comparison between the data obtained in the present study as compared to the work by Boon et al. [14].

Momentum space similarity measures were also derived from B3LYP/6-31G* calculations. To that end, the one density matrix was first transformed to momentum space via the usual Fourier transform and their effect on the basis functions [27]. The diagonal elements thus are the $\pi_A(\mathbf{p})$ needed in (5). mQSM measures are computed using either k=0 or k=1. All mQSM are directly computed starting from ab initio calculations with the molecules aligned according to the TGSA scheme. This allows for maximal comparability with the rQSM data. It deserves mentioning that Kohn Sham DFT calculations with approximate functionals such as B3LYP are not the best path to momentum space quantities as was shown most elaborately by Hart et al. [28]. The reason is that DFT calculations do not lead to the true wave function but rather to a wave function for non-interacting particles that yield the exact electron density. So neither the wave function nor the one density matrix corresponds to a true interacting electronic system. Nevertheless we opt to include DFT results in order to be able to compare correctly QSM between coordinate and momentum space. We did check whether for the QSM using DFT or HF had a big influence and established only a minor effect although the effect on the momenta was indeed significant which agrees with the results reported by Hart et al. [28]. The mQSM are computed numerically using a combination of Gauss-Laguerre quadrature [29] for the radial part of the integration and a Lebedev grid [30] for the angular part. In all cases Laguerre polynomials up to order 100 were used and Lebedev grids with 1202 angular points. For all molecules integration of $\pi_A(\mathbf{p})$ led to absolute errors in the number of electrons below 0.0001.

Ab initio calculations were performed using Gaussian-03 [31] and all QSM calculations in coordinate space were performed using a combination of BRABO [32] and own programs. All calculations in momentum space were performed using own routines.

RESULTS AND DISSCUSION

After alignment of the molecules using the TGSA algorithm, the coordinate space Carbó indices with respect to the N-methylacetamide molecule were computed. These values are shown in Table 1, together with the Carbó indices calculated by Boon et al. [14]. As can be seen from Table 1, comparable similarity indices and trends were obtained from both the *ab initio* and the ASA electron densities, proving again the excellent results that can be obtained using the ASA method to obtain similarity measures [26].

Table 1. Carbó indices (R) for peptide isosteres with respect to N-methylacetamide based on coordinate space rQSM using either ab initio B3LYP/6-31G* densities (DFT) or ASA densities.

Molecule	*overlap* R_{AB} *(DFT)* [15]	*overlap* R_{AB} *(DFT)*	*Coulomb* R_{AB} *(DFT)*	*overlap* R_{AB} *(ASA)*	*Coulomb* R_{AB} *(ASA)*
trans-2-butene	0.582	0.605	0.941	0.607	0.942
cis-2-butene	0.506	0.488	0.933	0.491	0.933
(Z)-2-fluorine-2-butene	0.418	0.671	0.981	0.672	0.981
Butane	0.466	0.511	0.933	0.511	0.932
ethylmethylthioether	0.034	0.110	0.741	0.110	0.742
Butanone	0.531	0.731	0.980	0.733	0.979
N,N-ethylmethylamine	0.412	0.567	0.938	0.566	0.938

From the results it can be noticed that, in general, the values for the overlap Carbó indices obtained in

this work are larger than the ones obtained by Boon et al. [14], due to the fact that the TGSA alignment superposes a higher number of atoms. A special case is the cis-2-butene molecule, for which the similarity index using the TGSA alignment method is lower than the one obtained by Boon et al.

The sequence for the coordinate space ab initio calculated overlap similarity indices with respect to N-methylacetamide and using the TGSA alignment is (see third column, Table 1): butanone > (Z)-2-fluorine-2-butene > trans-2-butene > N,N- ethylmethylamine > butane > cis-2-butene > ethylmethylthioether, which can be directly compared with the one obtained by Boon et al. (second column, Table 1): trans-2-butene > butanone > cis-2-butene > butane > (Z)-2-fluorine-2-butene > N,N-ethylmethylamine > ethylmethylthioether.

We observe that evidently both trends are different: this is a direct consequence of the difference in the alignment algorithm. From the present results, the most related molecule to N-methylacetamide is butanone; due to the fact that butanone and N-methylacetamide are the two only molecules of the set that have the carbonyl function, and in this way, the high electron density of oxygen atoms and the presence of π electrons of the double bond at the same position of space, make these molecules have a large similarity (Boon et al. found butanone in second position, only under trans-2-butene).

Following the order in overlap similarity comes (Z)-2-fluorine-2-butene, which can be explained by the similar characteristics of oxygen and fluorine atoms (both have major electronic densities compared with the other atoms of both molecules and both have an electron attractor behavior) and the presence of the trans double bond which can mimic the resonance characteristic of the amide bond in N-methylacetamide. This last feature can also count for the resemblance between N-methylacetamide and the following molecule of the list: trans-2-butene.

As noted above, an interesting case is cis-2-butene: for the alignment made by Boon et al. [14], this molecule is the third in the sequence while in this work it is found in the penultimate position. We explain this via the fact that in the previous work, the alignment method just takes in account the presence of the double bond, but not its configuration. On the other hand, TGSA looks for the best

matching sets of atoms and the opposite configuration of both bonds makes it impossible to align all heavy atoms of both molecules as in the case of butanone or butane with respect to N-methylacetamide (Figure 2C). TGSA identifies a different substructure as best matching, hence the possibility that the similarity is lower. Clearly, manual alignment as performed by Boon et al. and TGSA alignment can lead to significantly different results. If the similarity measures obtained from both different alignment algorithms have to be used further, for example for deciding which molecule would be the best candidate to replace N-methylacetamide for some purpose, this dependence on the alignment step is very undesirable. Bultinck et al. [7] therefore introduced the QSSA algorithm that aligns two molecules by maximizing the QSM using a genetic algorithm and a local optimizer. However, this algorithm, despite giving internally consistent globally maximal similarities [26], has the big drawback that the alignments that lead to the highest similarity are the result of overlapping the heaviest atoms and not necessarily the most similar functional groups.

According to the works by Allan and Cooper and co-workers [15-17], quantum similarity in momentum space could provide an answer to both drawbacks. First of all, in momentum space the largest densities are associated with the valence electron regions, which is exactly the region where most chemistry is located including most likely also the effects that lie at the basis of isosterism. A second advantage is that the exact alignment used is most likely less important. First of all because no translation is needed and second, the rotational alignment is most likely less influential due to the gerade symmetry of momentum densities. For the calculation of the mQSM we used the Fourier transform on the DFT one density matrices [27] obtained for the molecules in TGSA alignment with respect to N-methylacetamide. This is similar in concept as in the work by Allan and Cooper on propane, dimethylether and dimethylthioether [15] where the molecules are also aligned first at the coordinate space SCF stage in a way very similar to what is done in TGSA. For both k=0 (overlap mQSM) and k=1, the $D_{AB}^{m}(k)$ indices are shown in table 2. The reason for switching to these squared distances rather than Carbó indices is that the values for the latter are all very close to each other

whereas the Euclidean distances have a somewhat larger spread. To allow comparison with coordinate space data, table 2 also shows the $D_{AB}^{r}(\delta)$ (overlap rQSM) and $D_{AB}^{r}\left(\left|\mathbf{r}_1-\mathbf{r}_2\right|^{-1}\right)$ (Coulomb rQSM) values.

Table 2. Carbó indices (R) and squared Euclidean distances (D) for peptide isosteres with respect to N-methylacetamide based on momentum space mQSM.

Molecule	$D_{AB}^{m}(0)$	$D_{AB}^{m}(1)$	$D_{AB}^{r}(\delta)$	$D_{AB}^{r}\left(\left\|\mathbf{r}_1-\mathbf{r}_2\right\|^{-1}\right)$
trans-2-butene	0.76	1.03	151.56	81.37
cis-2-butene	0.72	1.01	192.07	88.65
(Z)-2-fluorine-2-butene	0.14	0.16	158.46	23.06
Butane	0.71	0.83	184.16	84.63
ethylmethylthioether	0.97	0.93	1043.82	374.81
Butanone	0.35	0.29	119.35	23.95
N,N-ethylmethylamine	0.40	0.54	170.46	76.61

Several things can be learned from table 2. First of all, there is a very similar trend in similarity between $D_{AB}^{m}(0)$ and $D_{AB}^{m}(1)$ with a linear regression coefficient of roughly 0.87. Apparently in this case, the inclusion of the momentum as an operator has very little effect. Although based on only three points, thereby rendering linear regression useless, Allan and Cooper found the same for propane isosteres. There is a very large difference in trend between that in $D_{AB}^{m}(0)$ and $D_{AB}^{r}(\delta)$. Whereas in coordinate space there was a very large distance between ethylmethylthioether and N-methylacetamide this has decreased to a value that is much closer to the other distances although it is still the most

distance molecule from N-methylacetamide. The most likely reason for the large distance in the overlap rQSM is the presence of a large core in the sulphur atom with high electron density. Even when ignoring this molecule, there is no correlation between $D_{AB}^{m}(0)$ and $D_{AB}^{r}(\delta)$, thereby leading to the conclusion that both similarity measures effectively reveal different information. A similar lack of meaningful correlation is found between $D_{AB}^{m}(0)$ and $D_{AB}^{r}\left(|\mathbf{r}_1-\mathbf{r}_2|^{-1}\right)$. Given the good correlation between $D_{AB}^{m}(0)$ and $D_{AB}^{m}(1)$, it is immediately clear that $D_{AB}^{m}(1)$ does not correlate with any of the coordinate space indices. Table 2 also allows checking the correlation within coordinate space between the two indices $D_{AB}^{r}(\delta)$ and $D_{AB}^{r}\left(|\mathbf{r}_1-\mathbf{r}_2|^{-1}\right)$. There is again no meaningful correlation if one takes into account the outlier nature of ethylmethylthioether. The linear regression coefficient $\left(R^2\right)$ is only 0.55, meaning no correlation. As a result, table 2 reveals that there are three sufficiently orthogonal sets of indices, namely $D_{AB}^{r}(\delta)$, $D_{AB}^{r}\left(|\mathbf{r}_1-\mathbf{r}_2|^{-1}\right)$ and either one of the two momentum space indices. The question then naturally arises what is the best index. This question cannot be answered generally as the answer will depend on the goal for which these similarity indices are to be used. It is then up to the user to judge what would be the most appropriate similarity measure for the goals at hand.

In order to have a better insight in the performance of the methods, we also report the case considered by Allan and Cooper for propane versus dimethyleter and dimethylthioether. The use of the moiety –S- as a replacement for a $–CH_2-$ unit is quite common in drug design as it leads to similar biological activity and possibly avoids some undesired side effects. The –O- moiety usually does not lead to similar activity. One can thus expect, assuming that the interactions in drugs are governed by electronic effects as a main contributor, that a good combination of the space in which similarity is computed, the operator used and the alignment algorithm would lead to the highest similarity between propane and the thioether and reduced similarity between propane and the ether. Again B3LYP/6-31G* densities were used, combined with TGSA alignment. The data obtained are shown in table 3.

Table 3: Similarity indices for dimethyleter and dimethylthioether versus propane.

Molecule	$D_{AB}^{m}(0)$	$D_{AB}^{m}(1)$	$D_{AB}^{r}(\delta)$	$D_{AB}^{r}\left(\lvert\mathbf{r}_1-\mathbf{r}_2\rvert^{-1}\right)$
dimethyleter	0.696	0.507	86.94	18.35
dimethylthioether	0.157	0.209	890.14	221.09

Several striking observations can be made. First of all, both momentum indices clearly indicate the thioether as most similar to propane, which agrees what in drug design would be expected. On the other hand, in coordinate space the results are completely opposite despite TGSA giving the expected alignment (maximal alignment of the CXC triad with X=C or O,S). The difference in geometry, however, is such that the atomic cores cannot be aligned perfectly and clearly the core electron densities have a huge effect on the similarity indices. This very nicely justifies the interest in momentum space similarity as there mainly the valence density is taken into account, which ultimately is also the region where the interaction with receptors as in drug interactions take place.

CONCLUSIONS

It has been shown that for the set of peptide isosteres considered here, many different user-made decisions can have a big influence on the resulting similarity orderings of the molecules. First it was shown that the alignment scheme used may have a substantial influence on the computed quantum similarity measures. Second, the choice of the operator used in the quantum similarity measure also has an important effect.

In a second part, quantum similarity measures were computed in momentum space using two different quantum similarity expressions. The resulting overlap type and first order moment quantum similarity measures reveal the same information but completely different information compared to what was

found in coordinate space.

In the third part the case of propane derivatives was examined where, based on knowledge of drug design, the similarity ordering is relatively easily predicted. Only the momentum space similarity indices predict nicely the expected similarity ranking which is related to the dominance of the valence density in the similarity integrals.

Concluding, quantum similarity measures depend to important extent on several decisions, such as the alignment scheme used, the operator used in the quantum similarity expressions and the space in which the similarity is measured. Users of quantum similarity should be very well aware of all these aspects and make well judged decision on what to use for specific goals.

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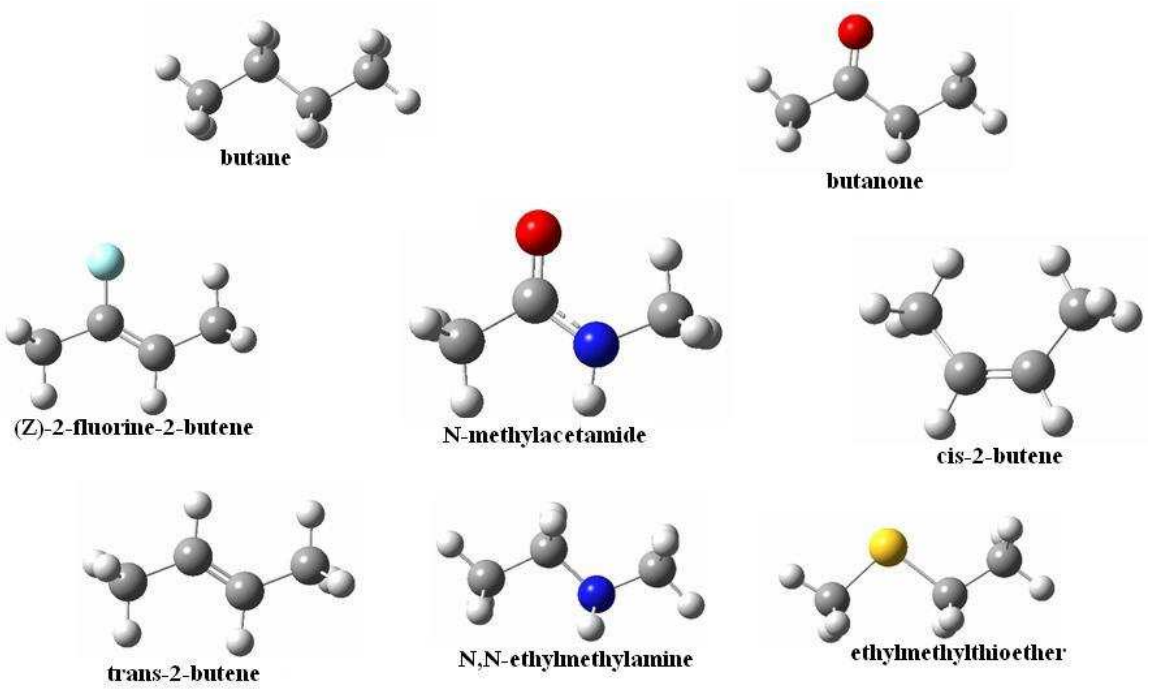

Figure 1. N-methylacetamide and peptide isosteres.

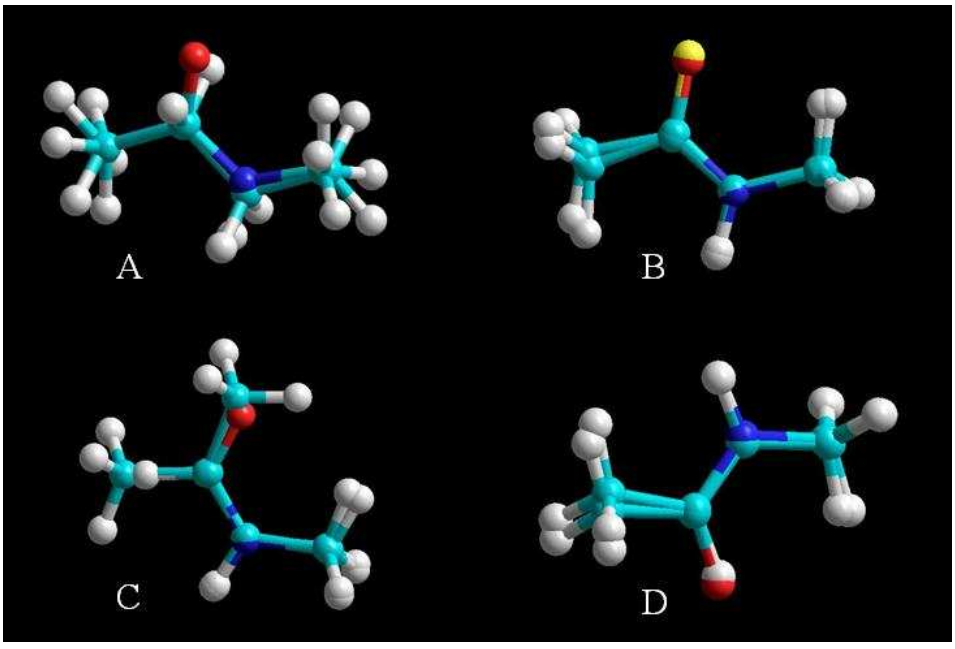

Figure 2. Alignment between N-methylacetamide and the peptide isosteres: A. butane; B. (Z)-2-fluorine-2-butene; C. cis-2-butene; D. trans-2-butene, using the TGSA algorithm.